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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/727,770	LI ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 October 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *4,8,9 and 24-29*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Continuation of 5. does NOT place the application in condition for allowance because:

Claims 4, 8, 9 and 24-29 are rejected under 35 USC §101 and 112, first paragraph, because the claims are not supported by a specific and substantial asserted utility or a well-established utility.

In response to the *prima facie* case and arguments of record, applicant first asserts that the Examiner's position that the homology disclosed in the present specification does not render the specific and substantial utility of the claimed invention readily apparent to the skilled artisan is made without factual evidence. On the contrary, the paragraph bridging pages 4-5 of the Office Action mailed 24 February 2003 states:

> Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick *et al.* (2000) *Trends Biotechnol.* 18:34-39 teach that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating specific details of protein function (see Box 2, page 36). Similarly, Bork (2000) *Genome Res.* 10:398-400 teaches that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially page 399). Smith *et al.* (1997) *Nature Biotechnol.* 15:1222-1223 teaches, "[t]ypical database searching methods are valuable for finding evolutionarily related proteins, but if there are only about 1000 major superfamilies in nature, then most homologs must have different molecular and cellular functions" (second column on page 132). These teaching demonstrate the unpredictability of assigning protein function based on structure alone.

Thus, the Examiner's position is indeed based on factual evidence regarding the lack of reliability of homology data as a means to ascribe specific function to a protein.

In reply to the Examiner's contention that the Hmmer results presented in the specification do not adequately disclose the specific functional characteristics of the claimed

invention such its utility is readily apparent to the skilled artisan because they are presented with no explanation as to their significance, Applicant urges that one of that the skilled artisan would know how to interpret the Hmmer results using publicly available software. The Examiner is aware of the public availability of this software and, in evaluating the disclosure, attempted to use the available Internet resources to answer the questions set forth in the previous Office Action. Specifically, "Does every polypeptide for which an Hmmer search returns a score of 14.8 and a description of 'ATP synthase subunit C' have a specific and substantial utility? What is the meaning of the parsed data? The score for domain 2 is almost twice as high as the score for domain 1. Does this mean that the protein is more likely to have the domain 2 function? If so, do all proteins that have domain 2 function have a specific and substantial utility even in the absence of domain 1?" None of the answers to these questions were readily apparent to the Examiner based on this evaluation. Applicant urges, "the Hummer search result shows that the protein of the present invention has a statistically significant domain of ATP synthase subunit C." However, even if this is assumed to be true, *arguendo*, the presence of "a statistically significant domain of ATP synthase subunit C" does not support a well-established utility for the claimed invention without knowledge the functional properties of that domain in the context of the rest of the protein and how those properties can be applied to a specific "real-world" use.

Applicant urges that the finding that even at 52% homology with the tomato vacuolar proton translocating peptide the peptide is identified as an ATPase evidences that the much higher homologies (71%) between the peptide of the invention and the human vacuolar ATP synthase would establish the present invention as an ATPase synthase, absent evidence to the contrary presented by the Examiner. As described above, factual evidence regarding the lack of

reliability of homology data as a means to ascribe specific function to a protein was provided in the 24 February 2003 Office Action. Applicant's assertion that the utility of the claimed invention would be readily apparent to the skilled artisan based on 71% homology between the protein of the invention and a human vacuolar ATP synthase because the invention exhibits 52% homology with a tomato vacuolar proton translocating ATPase appears to be based on flawed logic. First, the specific functional properties of the polypeptide encoded by the claimed nucleic acid would not be readily apparent to the skilled artisan based on either homology because homology is not a reliable predictor of function. Furthermore, Applicants' assertion that the 52% homology with the tomato protein establishes that the protein is an ATPase is unfounded because, as stated in the previous Office Action, "Applicant does not specifically identify any region in the tomato vacuolar proton translocating ATPase sequence as 'the vacuolar ATP synthase domain', or a region of particularly high sequence identity that would lead one to conclude that there is a conserved functional domain. In fact, the sequence alignment provided in the Exhibit is misformatted so that, even if there are regions of relatively high sequence identity, they are not apparent from the data provided" (page 5). Logically, proteins that are 52% or 71% identical do not share 100% functional identity; otherwise most proteins would be functionally redundant. Therefore, given the state of the art, a teaching of 52% or 71% identity does not establish the specific and substantial utility of a protein unless that disclosure is coupled with a disclosure of how the structural homology relates to the functional properties of the proteins (*i.e.*, which functions are shared and how the proteins are functionally different) and how the established function can be applied to a specific "real-world" use.

Next, Applicant alleges, "the Examiner stated, without presenting factual evidence that 'it is highly likely that it [the claimed invention] has other functions that are distinct form those of known ATP synthase subunits C.'" Applicant asserts that the Examiner has not provided any evidenced or teaching supporting that assumption of alternative activity that would contradict Applicant's assertion that the instant claimed polypeptide is indeed a vacuolar ATP synthase subunit. Applicant alleges that the Examiner appears to be requiring the Applicants to completely reduce to practice the claimed invention and to disprove his unsupported contention that the claimed invention has a different function.

Applicant's have misinterpreted the Examiner's position. First, with regard to the statement quoted by Applicant, which is found in the Office Action mailed 22 July 2004 (page 4) and, in context, reads:

> Given that even small changes in protein structure can produce significant changes in function, the skilled artisan would expect that the structural divergence of the claimed protein from proteins having established function would have some functional significance. Thus, even if the claimed invention did have some function in common with an ATP synthase subunit C, which is not established by the data presented in the specification, it is highly likely that it has other functions that are distinct from those of known ATP synthase subunits C. As the disclosure does not identify which functions of an ATP synthase are comprised by the polypeptide encoded by the claimed invention and provides no explanation of how the distinct structural characteristics of the claimed invention affect its function, the skilled artisan simply does not know what the specific functional characteristics of the claimed invention would be; therefore, the specification fails to provide a disclosure of the specific functional characteristics of the claimed invention such that the utility of the invention would be immediately apparent to the skilled artisan.

As discussed in the 22 July Office Action, a "well-established utility" is a specific, substantial and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material alone or taken with the knowledge of

one skilled in the art. As discussed above, it is reasonable to expect that proteins having distinct structure also have some distinct function, even if other functions are conserved. Therefore, a disclosure that a protein has some structural similarity to another protein does not suggest a "well-established" utility unless the structural properties are disclosed with sufficient correlation of structure to function such that the utility of the protein is readily apparent. Contrary to Applicant's assertion, the Examiner is not requiring that Applicant completely reduce to practice the claimed invention. What is required is a disclosure of the properties of the protein which alone or taken with the knowledge of one skilled in the art provide a specific, substantial and credible utility which is well known, immediately apparent, or implied by the said disclosure.

Applicant reiterates the argument that the skilled artisan would recognize how the specification teachings address a real world problem based on differential regulation of H^+-K^+-ATPases at the molecular level in acid-base and electrolyte disorders and teachings in the art indicating ATP synthases are known to function in cellular and physiological processes, are found in the plasma membrane of human tumor cells, involved in renal acidification bone resorption.

These arguments were addressed in previous Office Actions. As discussed in the 22 July Office Action (pages 6-7), the alleged assertion that the polypeptide encoded by the claimed nucleic acid is involved in acid-base and electrolyte disorders appears to be based on the physical proximity of the claimed invention to an H^+-K^+-ATPase and the disclosure does not establish that the particular protein encoded by the claimed nucleic acid is expressed on the plasma membrane of human tumor cells, is involved in renal acidification or functions in bone resorption; thus, even if some vacuolar ATP synthases have the recited properties, there is no

evidence that the protein at issue has any of these properties. Furthermore, even if one were to assume, *arguendo*, that the claimed protein is expressed on the plasma membrane of human tumor cells like the protein of Martinez-Zaguilan *et al.*, is involved in renal acidification like the protein of Brown *et al.* or functions in bone resorption like the protein of Chatterjee *et al.*, there is no specific utility that universally applies to all proteins having these properties and there is no basis in the disclosure for a specific and substantial utility for a protein having these properties. One of ordinary skill in the art does not know how to use a protein that is expressed on a human tumor cell unless that expression is established to be a viable diagnostic marker or target for anticancer therapy. One does not know how to use a protein involved in renal acidification or bone resorption unless it is known how the protein is involved in the process and how modifying the function or expression of the protein affects the process. Thus, not only does the specification fail to establish that the claimed invention has the properties of the proteins in the cited art, it fails to provide a specific and substantial teaching of how any protein having those properties can be used. These are not specific and substantial asserted utilities for the claimed invention but invitations to the skilled artisan to experiment and determine which, if any, of these utilities might be valid. "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner, Comr. Pats. v. Manson,* 148 USPQ 689 (US SupCt 1966) at 696.

Applicant also reiterates the position that the CCPA's finding in *Nelson v. Bowler*, 206 USPQ 881 supports the position that the claimed invention has useful value in the drug discovery process even though the molecule may not be associated with a specific treatment. This argument has been repeatedly addressed in previous Office Actions. In *Nelson*, the Court makes

clear that the utility of the16-phenoxy-substituted prostaglandins claimed by Nelson is supported by the demonstration of a pressor effect *in vivo* and the reasonable correlation of that effect to a "real-world" utility. This finding does not support Applicant's contention that a patentable utility requires only that the nucleic acid be useful in a drug discovery process even though the molecule is not associated with a specific treatment and/or diagnosis.

Likewise, Applicant asserts that the utility rejection conflicts with the case of *Juicy Whip v. Orange Bang* (Fed. Cir. 1999) and contends that the polypeptides and encoding nucleic acid molecules of the present invention are well-known in the art to be valuable drug targets and therefore have readily apparent commercial utilities, such as for screening potential drug compounds, producing antibodies, developing hybridization probes and primers, *etc.* However, as stated in previous Office Actions, the Examiner's position is not that the claimed invention will never be useful but that a specific and substantial utility for the claimed invention is not asserted in the application and is not readily apparent from the properties of the claimed invention that are disclosed. Utilities such as screening potential drug compounds, producing antibodies, developing hybridization probes and primers, *etc.* are generic to all nucleic acids and are not patentable utilities in the absence of teachings which identify specific utilities for the drug compounds, antibodies, primers and probes.

Applicant asserts that the basis to reject the instant claims is not present in *Brenner v. Manson* because the present claims are directed to a product and *Brenner v. Manson* pertains to process claims. However, as Applicant must surely be aware, the process at issue in *Brenner* was found to lack patentable utility because the product made thereby lacked patentable utility. With regard to the product, the Court considered an assertion that the compound has specific utility

based on a published article revealing that an adjacent homologue of the steroid yielded by the claimed process has tumor-inhibiting effects in mice and concludes, "even on the assumption that the process would be patentable were respondent to show that the steroid produced had tumor-inhibiting effect in mice, we would not overrule the Patent Office finding that respondent has not made such a showing. The Patent Office held that, despite the reference to the adjacent homologue, respondent's papers did not disclose a sufficient likelihood that the steroid yielded by his process would have similar tumor-inhibiting characteristics. Indeed, respondent himself recognized that the presumption that adjacent homologues have the same utility has been challenged in the steroid field because of 'a greater known unpredictability of compounds in that field'" (page 694).

Thus, Contrary to Applicant's assertion, the *Brenner* case is indeed applicable to the present claims. First, the court found that structural similarity to a compound having established function may not support patentable utility, particularly when, as in the instant case, the field recognizes that establishing function based on structural similarity is unpredictable. Second, the Court found that a process for making a product does not have patentable utility if the product made does not itself have patentable utility. By logical extension, an assertion that a product can be used in a process of making another product (*e.g.*, can be used to screen for potential drug compounds, producing antibodies, *etc.*) cannot be relied upon for patentability unless there is a disclosed or readily apparent specific and substantial utility for the products made using the claimed product.

Next, Applicant takes issue with the assertion that the specific utility of the claimed invention must actually be contemplated by the inventor. Applicant appears to find no basis in

law which would support a requirement that the inventor actually contemplate how his invention might be used.

First, Applicant is basing arguments on a fragment of a sentence quoted out of context. The statement cited was made in the Office Action mailed 20 November 2003 (page 9-10) was made in response to Applicant's contention that asserted utilities such as serving as targets for developing molecular probes and therapeutic agents and use as probes, primers, and chemical intermediates, particularly in biological assays, which are generic to all nucleic acids, are actually specific utilities because "such uses are specific for the claimed nucleic acid molecules, and the products of such uses will be clearly different (and hence specific for the claimed molecules) than what would be produced using a different nucleic acid molecule for the same purpose." In response, the Examiner states:

> These arguments are not persuasive because the teachings of the specification are merely broad recitations of what could be done with any nucleic acid. Any nucleic acid molecule can be used as a probe, a primer, or a chemical intermediate. Although it is true that in the instant case the probes, primers and final products would be unique to the instant nucleic acid, the utilities set forth in the specification are not based on the unique properties of the invention. For example, were the nucleic acid demonstrated to be linked to hypersecretion of stomach acid, the skilled artisan would know that the probes, primers and final products could be used to develop potential therapeutics for the treatment of esophagitis. That is not the case here. Instead, Applicant has disclosed a nucleic acid, the function of which is likely unknown, and teaches the skilled artisan that the nucleic acid is useful for the same things that any nucleic acid is useful for, because it is a nucleic acid. Applicant seems to be arguing that the specific utility of the invention is inherent to the nucleic acid and need not be described. This is akin to arguing that a teaching that a given transgenic mouse, comprising a specified gene, can be used as rat food constitutes a specific utility simply because the transgenic mouse is inherently different from other transgenic or wild type mice. Clearly this is not the case. A teaching of specific utility requires more than a general statement that a specific utility is likely to exist by virtue of the invention being different from other molecules belonging to the same class. Instead, the specific utility must actually be contemplated by the inventor.

Support for the Examiner's position as a whole can be found in various places. For example on page 8 of the same Office Action, the Examiner cites *In re Gardner, Roe and Willey* 166 USPQ 138, "[l]aw requires that disclosure in application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves." Further, it is well-established that the utility for the claimed invention must be either asserted in the specification or be well known, immediately apparent, or implied by the specification's disclosure of the properties of a material alone or taken with the knowledge of one skilled in the art. These alone supports the Examiner's contention that it is not sufficient to assert a utility that is generic to a broad class of invention and then assert that the utility is a specific utility because the invention has undisclosed properties that are different from other members of the broad class. The Examiner's contention is that the specific properties of the invention that distinguish it from other members of the broad class must be disclosed if they are to be relied upon to establish a specific utility.

Finally, Applicant reiterates previous assertions that disclosure of the function of the transporter is sufficient and that by placing a new member of the transporter protein family into the public domain the invention enables significant advancement in medicine and discovery. These arguments are not deemed persuasive because, for reasons stated in previous Office Actions and herein above, Applicant has not, in fact, disclosed the function of the claimed invention such that a specific and substantial utility would be apparent to one of ordinary skill in the art and Applicant is seeking a grant of patent rights for a product which has not been developed and pointed to the degree of specific utility, which would create a monopoly of knowledge not clearly commanded by the statute.

Applicant's arguments have been fully considered but, upon careful consideration of the record as a whole, are not deemed persuasive. Therefore, the claims stand rejected under 35 USC §101 and 112, first paragraph, as lacking support of a specific and substantial asserted or well-established utility.

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